Red Cell Volume Expansion at Altitude: A Meta-analysis and Monte Carlo Simulation

PETER RASMUSSEN[1,2,3], CHRISTOPH SIEBENMANN[1,2], VÍCTOR DÍAZ[1,4,5], and CARSTEN LUNDBY[1,2]

[1]Zurich Center of Integrative Human Physiology, Institute of Physiology, Zurich, SWITZERLAND; [2]Institute of Physiology, University of Zurich, Zurich, SWITZERLAND; [3]Department of Neuroscience and Pharmacology, University of Copenhagen, Copenhagen, DENMARK; [4]Institute of Veterinary Physiology, University of Zurich, Zurich, SWITZERLAND; [5]Department of Health and Human Performance, Faculty of Sport Science–INEF, Technical University of Madrid, Madrid, SPAIN

ABSTRACT

RASMUSSEN, P., C. SIEBENMANN, V. DÍAZ, and C. LUNDBY. Red Cell Volume Expansion at Altitude: A Meta-analysis and Monte Carlo Simulation. *Med. Sci. Sports Exerc.*, Vol. 45, No. 9, pp. 1767–1772, 2013. **Introduction**: Altitude acclimatization is associated with a rapid increase in hematocrit. The time course and the contribution of the red cell volume expansion are not clear. The purpose of the present meta-analysis was to explore how much altitude exposure is required to induce polycythemia in healthy lowlanders. **Methods**: A systematic review was performed of 66 published articles (including 447 volunteers) identified through literature search. We performed a mixed-model random-effects meta-analysis and a Monte Carlo simulation on the extracted data. **Results**: The following results were obtained in this study: 1) the red cell volume expansion for a given duration of exposure is dependent on altitude ($P < 0.0001$), that is, that the increase in red cell volume was accelerated at higher altitudes; and 2) the extent of the erythropoietic response depends on the initial red cell volume ($P < 0.0001$). It seems that exposure time must exceed 2 wk at an altitude of more than 4000 m to exert a statistically significant effect. At lower altitudes, longer exposure times are needed with altitudes lower than 3000 m not yielding an increase within 4 wk. **Conclusions**: Red cell volume response to hypoxia is generally slow, although it accelerates with increasing altitude. This, in combination with a dependency on initial red cell volume, suggests that, for example, athletes may need to spend more time at altitude to see an effect on red cell volume than commonly recommended. **Key Words:** ALTITUDE TRAINING, HEMOGLOBIN MASS, HYPOXIA, SYSTEMATIC REVIEW

Hypoxia leads to the stabilization of the hypoxia inducible factor 2 system in the renal peritubular cells, which subsequently binds to the hypoxic response element on the erythropoietin (Epo) gene and induces synthesis and release of Epo (13). As a result, plasma Epo concentrations start to increase after approximately 2 h of hypoxic exposure (6). As exposure continues, a zenith is reached after 3–4 d, where after-plasma Epo concentration gradually decreases to stabilize values slightly above sea level (3,23,29).

The primary function of Epo is to regulate red blood cell volume by promoting the proliferation and differentiation of erythrocytic progenitors, and because permanent residence at altitude is associated with an augmented total red cell volume (RCV) (29), the paradigm has evolved that extended hypoxic exposure induces polycythemia in lowlanders. Nevertheless, the Epo response to hypoxia does not necessarily translate into an elevated RCV (1,27). In fact, the initial increase in hematocrit at altitude is entirely the result of a plasma volume contraction that occurs within the first hours or days of exposure (26). In contrast, the time course of RCV expansion and the dependency on the degree of hypoxia remain largely unknown. This is related to the inconvenience of exposing a sufficient subject number to different altitudes for a prolonged time. To overcome this problem, we conducted a meta-analysis of published experiments and explored the altitude exposure and duration thereof required to induce polycythemia in healthy lowlanders.

METHODS

Search Strategy. This meta-analysis is based on articles retrieved from the Web-based databases PubMed and Web of Science (see Supplementary Digital Content, http://links.lww.com/MSS/A266). Up to January 2012, we introduced the following key words and Boolean connectors: (altitude OR hypoxia) AND acclimatization AND (hemoglobin mass OR hemoglobin mass OR hematocrit OR hematocrit OR red blood cell mass OR red blood cell volume OR blood volume OR plasma volume).

The search was refined by applying the limits "Humans" and "All adult: +19 years" in PubMed and searching within the subject areas of physiology, respiratory system, cardiovascular system cardiology, sport sciences, and hematology in the Web of Science. This initial search generated a group of 6775 references that were transferred to an EndNote (Thomson Reuters, New York, NY) database.

In EndNote, duplicate references were removed. From the remaining references *in vitro*, animal, or high altitude natives studies, reviews and conference proceedings were eliminated. The abstracts of the 446 remaining articles were then independently evaluated by two researchers, and articles not fulfilling the eligibility criteria (see next section) were removed. Disagreements were resolved by involving the rest of the research team. By this process, 53 articles were selected.

Subsequently, we built a reference map for each article and obtained the references cited in or citing the initial 53 articles. This step retrieved a new group of 3185 articles (1503 backward and 1682 forward references), and the same process detailed earlier and in Figure 1 was repeated. Finally, 66 articles were selected to be included in the meta-analysis (see Supplementary Digital Content, http://links.lww.com/MSS/A266).

Eligibility criteria. Any study on healthy humans reporting data before and after a period of exposure to hypoxia (normobaric or hypobaric, continuous or intermittent) for blood compartments (plasma volume, RCV, or blood volume) or total hemoglobin mass was eligible. Only investigations using direct methods of measurement (Evans blue, carbon monoxide rebreathing, radioiodinated albumin, or brilliant red dilution) were accepted. Studies in which the experimental procedures included any intervention susceptible of affecting any blood compartment, other than physical activity, were eliminated as well.

Data extraction. The data were transferred into an Excel file by two researchers working independently and subsequently compared with avoid errors. When data were extracted from the figures, the mean between the values obtained by the two researchers was taken.

When altitude was not constant, a time-weighted average was calculated.

$$\text{Average altitude} = \frac{\sum_{i=1}^{n} \text{Dur}_i \times \text{Alt}_i}{\text{Total duration}} = \frac{\text{Dur}_1 \times \text{Alt}_1 + \text{Dur}_2 \times \text{Alt}_2 + L + \text{Dur}_n \times \text{Alt}_n}{\text{Total duration}}$$

where Dur_i and Alt_i are the duration and altitude at step i. So for, for example, a stepwise accent to Mount Everest (24), the average altitude is derived as [1 d × 3800 m + 5 d × 4500 m + 5 d × 5000 m + 2 d × 5500 + ⋯] / 36 d = 5720 m. If only SEM values were reported, variance was calculated from sample size and SD; otherwise, variance was calculated from SD alone.

Statistical analysis. A mixed-model random-effects meta-regression was performed (SAS 9.2; SAS Institute Inc., Cary, NC) on log-response ratios (12). The log-response ratio was calculated as the logarithm to the change in RCV, that is, the postvalue divided by the prevalue/control value. We chose RCV as our effect parameter because of the linear relationship with hemoglobin mass, whereas hematocrit and hemoglobin concentrations were excluded for their dependency on plasma volume. If RCV was not reported, it was derived from hemoglobin mass according to a linear relationship derived from the 13 studies (n = 28) that reported both hemoglobin mass and RCV (RCV = hemoglobin mass × 2.899, $P < 0.0001$). In general, none of the included studies reported confidence intervals or SD on the change in RCV; rather, SD (or SEM) was reported on the pre- and postvalues separately. Variance was therefore corrected as proposed for crossover trials (5). P values <0.05 were considered statistically significant.

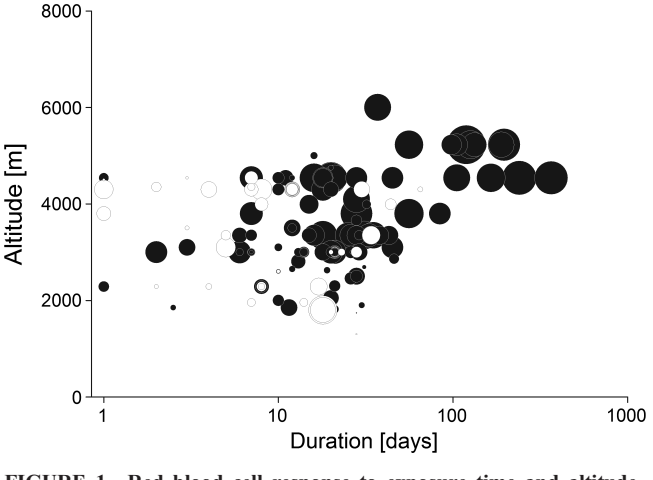

FIGURE 1—Red blood cell response to exposure time and altitude. Bubble sizes are scaled to log-response ratio and weighted according to study sample size to preserve presentation fidelity transformed with square root function. Filled bubbles indicate increased red cell increase, and open bubbles indicate decreases.

ANALYSIS AND RESULTS

Overall subject characteristics are reported in Table 1. In total, this analysis reports data from 447 volunteers of which 376 were men and 71 women. RCV increases versus exposure time and altitude are shown in Figure 1. Of the collected data, 75% documented an increase in RCV, that is, an effect size >0 regardless of statistical significance. Across the data set, average RCV increase per week was 49 ± 240 mL·wk^{-1}. Stratifying by exposure time, average RCV increases per week were 37 ± 81, 56 ± 21, and 100 ± 467 mL·wk^{-1} with 10, 20, and 28 d of exposure, respectively, across all altitudes. For altitudes higher than 3000 m, the corresponding values were 46 ± 53, 46 ± 258, and 188 ± 466 mL·wk^{-1}.

Heterogeneity. Because of the inclusion of articles spanning different methods (plasma dye dilution, carbon monoxide rebreathing, or radioactive albumin labeling), altitudes (from 1300 to 6000 m above sea level), exposure times (from 1 d to 1 yr), intermittent hypoxia (range 1–21 h·d^{-1}, mean 12 ± 5 h·d^{-1}), and normobaric hypoxia, data set heterogeneity is a potential confounder that might affect outcome of the analysis (Table 2). We tested for inhomogeneity

TABLE 1. Volunteer characteristics.

	5%	25%	Median	75%	95%
Hematocrit (%)	39.7	42.4	44.3	46.0	46.8
Body weight (kg)	56.5	58.9	66.1	72.6	74.1
[Hb] (mmol·L^{-1})	9.3	13.9	14.7	15.0	15.7
Hemoglobin mass (g)	654	733	868	988	1023
Per kg body weight	10.0	11.5	12.7	14.4	17.5
Plasma volume (mL)	2459	3019	3115	3536	4075
Per kg body weight	39.0	44.4	49.5	55.1	60.6
Red blood cell volume (mL)	1896	2125	2518	2864	2966
Per kg body weight	28.9	33.4	36.9	41.7	50.7
Total blood volume (mL)	4377	5410	5798	5979	7220
Per kg body weight	68.2	77.3	84.0	103.5	105.8

using a mixed-model regression analysis and found no significant effect of the measurement method (P = 0.94), normobaric versus hypobaric hypoxia (P = 0.68), continuous versus intermittent hypoxia (P = 0.14), or exercise versus no exercise (P = 0.23). Accordingly, all data were included in the main analysis.

Effect of altitude and duration of exposure. For clarity of presentation, data were divided into both altitude and duration quartiles (see Fig. 2). The random effects model yielded significant main effects for both altitude and duration (both $P < 0.0001$, Fig. 1); however, there was also a significant interaction effect ($P < 0.0001$), and therefore the main effects (P values indicated) should be interpreted with caution. It seems that exposure time must exceed at least 2 wk at an altitude of more than 4000 m to exert a significant effect. At lower altitudes, even longer exposure times are needed with altitudes lower than 3000 m not yielding a statistically significant result within 4 wk.

We subsequently performed Monte Carlo simulation to estimate the required exposure time for an increase in RCV at different altitudes. We entered mean pre- and postexposure RCV values with SD along with exposure time into a custom-written Matlab (MathWorks, Natick, MA) procedure. From these distributions, we randomly drew paired numbers and calculated changes in RCV as a function of time. The results of the simulation are presented in Table 3. There is an accelerating effect of increasing altitude so that, for example, reaching a 10% increase at 2000 m will take 42 to 145 d, whereas at 3500 m this can be achieved between 23 and 51 d.

Effect of initial RCV. Finally, we examined the effect of the initial RCV on the RCV response to hypoxic exposure. To obtain a homologous data set, that is, data obtained with comparable exposure and methodology, we restricted the analysis to the special case of exposure between 3000 and 3500 m and more than 7 d of stay. The random-effects model showed a highly significant effect of initial RCV with a high initial RCV showing less increase compared with low initial RCV ($P < 0.0001$, Fig. 3).

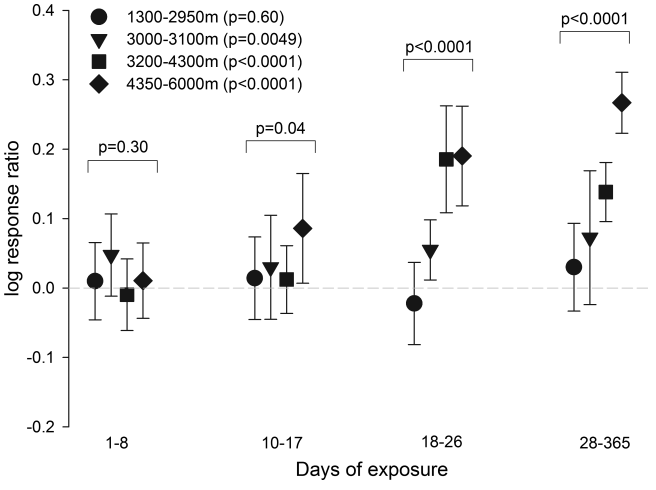

FIGURE 2—Red blood cell response. Data are presented in altitude and exposure quartiles. Note that there was a significant interaction between the effect of attitude and the exposure duration ($P < 0.0001$); therefore, the main effects (P values indicated) should be interpreted with caution. It is, however, clear that exposure time must exceed 17 d at an altitude of more than 4000 m to exert a significant effect on the oxygen carrying capacity of the blood. Data are weighted log-response ratios with error bars indicating 95% confidence intervals.

DISCUSSION

The main findings of the meta-analysis and Monte Carlo simulations are that altitude exposure must exceed 2 wk at an altitude of >4000 m to exert a significant effect on RCV. At lower altitudes, even longer exposure is required with altitudes lower than 3000 m not yielding a statistically significant result within 4 wk. Thus, we established an altitude dose–response curve, indicating that the hypoxia-induced response in RCV may be slower than widely expected (30).

Variation in RCV response. We found that the average RCV increase per week for our data was 49 ± 240 mL·wk^{-1}, which, on average, is in accordance with previous findings with EPO administration (2). Although we find the large variation surprising, similar results may be found in the plasma Epo response to altitude. Ge et al. (10) reported that the increase in plasma Epo after 24 h at 2800 m varied markedly among individuals (n = 48), ranging from

TABLE 2. No. data points entering the analysis depending on methodology.

	N	Pct.	CO Rebreathing	Plasma Dye Dilution	Radiolabeled Albumin	Hypobaric Hypoxia	Normobaric Hypoxia	Continuous Hypoxia	Intermittent Hypoxia
CO rebreathing	67	44.1	—	—	—	—	—	—	—
Plasma dye dilution	56	36.8	—	—	—	—	—	—	—
Radiolabeled albumin	29	19.1	—	—	—	—	—	—	—
Hypobaric hypoxia	120	79.0	35	56	29	—	—	—	—
Normobaric hypoxia	32	21.1	32	0	0	—	—	—	—
Continuous hypoxia	111	73.0	31	52	28	111	0	—	—
Intermittent hypoxia	41	27.0	36	4	1	9	32	—	—
No exercise	92	60.5	22	52	18	92	0	91	1
Exercise	60	39.5	45	4	11	28	32	20	40

TABLE 3. Exposure time in days to obtain 95% probability for an increase in red blood cell volume.

	Altitude			
Both Continuous and Intermittent Hypoxia	**2000**	**2500**	**3000**	**3500**
1.00%	27 (21–39)	22 (18–32)	24 (18–31)	20 (12–38)
2.50%	35 (27–46)	25 (20–36)	26 (21–32)	20 (13–40)
5.00%	45 (33–60)	32 (28–44)	30 (26–38)	22 (17–41)
7.50%	59 (37–94)	42 (35–56)	33 (28–42)	23 (21–47)
10.00%	85 (42–145)	49 (39–116)	37 (31–46)	26 (23–51)
Only continuous hypoxia				
1.00%	30 (24–44)	18 (14–23)	21 (13–28)	20 (12–40)
2.50%	38 (31–48)	20 (16–26)	21 (15–28)	21 (13–38)
5.00%	52 (37–72)	29 (22–34)	23 (19–30)	22 (17–41)
7.50%	69 (40–99)	34 (25–47)	24 (21–33)	23 (21–45)
10.00%	95 (47–141)	37 (28–49)	26 (23–37)	26 (22–52)

Monte Carlo simulation, 50,000 simulations; each altitude spans 375 m on each side of the midpoint. Numbers in parentheses are the 5th–95th percentile range.

−41% to 400%, which seemed mainly governed by upstream factors related to renal parenchymal PO_2, although genetic factors cannot be ruled out (19). Although variations in both RCV and the Epo response to altitude are observed, these do not seem to be interlinked. In a retrospectively analysis (16), no correlation between EPO and erythropoietic response was observed, which points to interindividual variation in responsiveness (4). The Epo-induced expansion of RCV can be used as a measuring stick for the speed of which RCV expands at altitude. Previous findings with Epo suggest that RCV expansion would not be expected to exceed 50 mL·wk^{-1} (2); however, we found that >35% of the reported data correspond to RCV increases per week in excess of 50 mL·wk^{-1}, and this finding is in accordance with Sawka et al. (26). It is intriguing that, in some studies, an increase in RCV is observed within days of exposure to an altitude that did not stimulate polycythemia even after weeks in other studies (Fig. 1). This suggests a substantial interindividual variation (27). Other candidates that could lead to variation include the use of different measurement techniques or of the application of continuous versus intermittent or normobaric versus hypobaric hypoxia (Table 2). Although there was no systematic effect observed when these parameters were entered as factors, the inclusion of results obtained with different methods may have increased the variance and reduced the power of the analysis. Some evidence suggests slightly different physiological responses to hypobaric versus normobaric hypoxia about ventilation and acute mountain sickness (18,22). However, this does not seem to be the case for the RCV response, which is in line with the observation that the Epo response to hypobaric and normobaric hypoxia is also similar (7).

Effect of initial RCV. One factor that affected the response to altitude exposure was the initial RCV. In this context, we recently failed to observe an increase in RCV after 16 h·d^{-1} at 3000 m for 4 wk (27). From the analysis, we would expect a 5%–10% increase in RCV, and we speculated (25) that the absence of an increase in RCV could be related to the high initial hemoglobin mass of the included elite athletes that were at the upper end of physiological range (Table 1). The present meta-analysis supports this approach (Fig. 3). Although it is intuitively straightforward that an upper limit to RCV expansion must exist, the physiological mechanism governing such a limit is not as easily explained. Although the current meta-analysis indicates that a high initial RCV limits a further expansion in hypoxia, the study by Kapoor and Chatterjee (15) pointed out that despite a high baseline level, an increase in RCV can still occur if duration and altitude are sufficient (Fig. 1). Thus, to what extent a physiological upper limit to RCV exists is not clear from this meta-analysis. However, 17.5 g of hemoglobin per kilogram bodyweight has been reported in World and Olympic Champion cross-country skiers (14), which is markedly higher than the values reported in healthy but untrained high altitude Peruvians (8). Thus, the upper limit is likely not reached by altitude exposure alone. It should thus be considered that an RCV ceiling may not relate to increased oxygen carrying capacity of blood alone. Any such ceiling could also be related to an upper limit in blood volume and thereby to blood pressure regulation.

Another explanation for the finding that a high initial RCV attenuates the further increase with hypoxic exposure could be the statistical phenomenon of regression toward the mean. Regression toward the mean may occur when RCV is

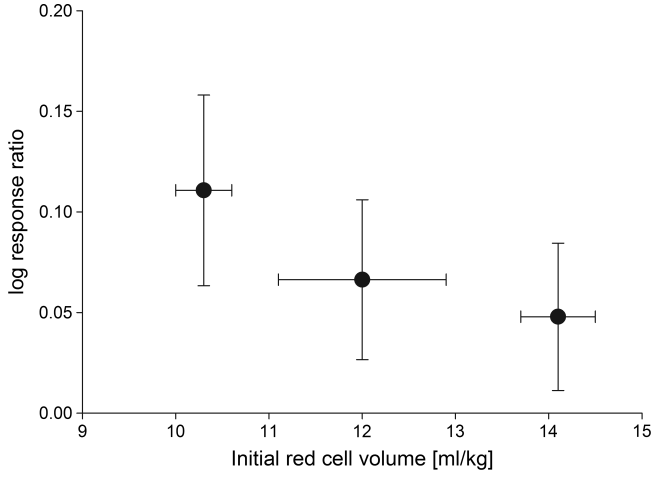

FIGURE 3—The effect of initial hemoglobin mass on response to hypoxic exposure. To ensure clarity of presentation and to avoid confounding bias, data are limited to exposure times between 7 and 40 d at altitudes between 3000 and 3500 m. On the abscissae, log-response ratios with 95% confidence intervals are presented and on the ordinate hemoglobin mass with SD. Mean values for altitude (3327, 3097, and 3070 m) and exposure (21, 19, and 23 d) for the three hemoglobin mass groups (N = 13, 14, and 15) are not different.

high on its first measurement because it will by chance tend to be closer to the average on a second measurement. To avoid drawing wrong conclusions from this meta-analysis (particularly Fig. 3), the possibility of regression toward the mean should be considered. However, because regression toward the mean is not based on cause and effect, but rather on random error in a natural distribution around a mean, we cannot exclude any underlying physiological mechanisms influencing the effect of initial RCV on erythropoietic response to altitude exposure.

Is altitude exposure relevant for athletes? To increase RCV and thereby also sea-level exercise performance, it is recommended that athletes reside in normobaric or hypobaric hypoxia corresponding to an altitude of 2500–3000 m for a minimum of 14 $h \cdot d^{-1}$ for 3 wk (30). The effect of the initial RCV (Fig. 3) and the considerable time required to establish an RCV response to medium altitude exposure (Table 3) are of relevance for athletes considering engaging into altitude training. Assuming that anecdotal reports of athletes coping poorly with altitudes higher than 3000 m (increased recovery period after exercise, poor quality of sleep, etc.) are correct, then altitudes above this threshold should be avoided. Because only studies in athletes who have demonstrated >5% increase in hemoglobin mass after altitude training generally report an increase in exercise performance (25), it is recommended that athletes should spend sufficient time at altitude to achieve a corresponding increase in hemoglobin mass. A gain in hemoglobin mass of 7.5% requires between 35 and 56 d of live high–train low or 25 to 47 d of continuous exposure at 2500 m to achieve a >95% probability for an increase (Table 3). This may be further extended by a high initial RCV, which results in lower probability for a further increase to occur. This questions the feasibility of altitude training for elite athletes, and the potential gains by altitude training, at least in athletes with a high RCV starting point, should therefore be carefully reconsidered.

Publication bias. We found some indications of publication bias in the tendency for studies with small changes and large variations to be missing from the analysis. Thus, we cannot exclude that the analysis overestimates the positive outcome. On the other hand, almost 40% of the included data points reported negative findings and 50% of the data points reported less than 2.5% increase.

Data set heterogeneity. Roughly a fourth of the data originates from studies involving intermittent hypoxia (Table 2). We were not able to detect any significant differences when the two hypoxic exposures were compared in the random-effects model. However, Monte Carlo analysis revealed that when the data obtained from intermittent hypoxic exposure were removed from the analysis, time to a 95% chance for an increase in RCV generally decreased with 4–7 d, particularly around 3000 m above sea level where most of the intermittent hypoxia studies were performed. We also recorded iron supplementation, and in 72% of the studies, no iron supplementation was performed. Levine and Stray-Gundersen (17) suggested that iron supplementation is needed only if iron stores are low. Parisotto et al. (20) could not find an effect of iron supplementation when Epo was administrated. Thus, iron availability may not be an issue for healthy individuals. However, it is still not straightforward to access the impact of iron supplementation as, for example, most studies with iron supplementation use intermittent hypoxia. Thus, there is a risk of covariance between the parameters. This extends to possible differences between normobaric and hypobaric hypoxia, sex, and methods used. In general, we saw no indications that normobaric hypoxia was producing a different response than hypobaric hypoxia, which is in accordance with our recent findings (21). Likewise, we were not able to detect any differences between the few studies reporting only women and those with only men or a mixed population. What we note, however, is that to our knowledge, no studies have looked specifically at sex differences in RCV response to altitude dwelling, and very few studies report males and females separately. Finally, the method to estimate RCV may also introduce bias. According to Sawka el al. (26), CO rebreathing may overestimate not only the RCV but also the changes in RCV after altitude exposure because of CO loss to myoglobin or other iron porphyrin molecules (i.e., in the liver) and according changes in the quantity of these molecules after altitude exposure. However, Gore et al. (11) and Thomsen et al. (28) concluded that the two measurements were equivalent. Furthermore, CO loss to myoglobin is assumed minimal (1.6 mL for 10 min [9]), and even if myoglobin should change because of altitude exposure, the effect hereof on RCV must be assumed neglectable. Finally, it is unknown if these extravascular iron molecules actually increase with hypoxic exposure.

CONCLUSIONS

The physiological process of red cell expansion occurs relatively slowly with only minor chances for an increase to occur within 2 wk and exposure times longer than 4 wk generally required. Also, the accepted paradigm that altitudes <3000 m are sufficient to trigger a robust RCV should be reconsidered, particularly if the initial RCV is high. This, in combination with a dependence on initial RCV, suggests that, for example, athletes may need to spend more time at altitude to see an effect on RCV than commonly recommended.

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Peter Rasmussen, Christoph Siebenmann, and Víctor Díaz contributed equally to the manuscript.

C.L. initiated the investigation; P.R. and V.D. designed the literature search; C.S. and V.D. extracted the data; and P.R. performed the analysis. All authors wrote the article and approved the final version.

The authors declare no conflict of interest.

The results of the present study do not constitute endorsement by the American College of Sports Medicine.

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Supplemental Digital Content

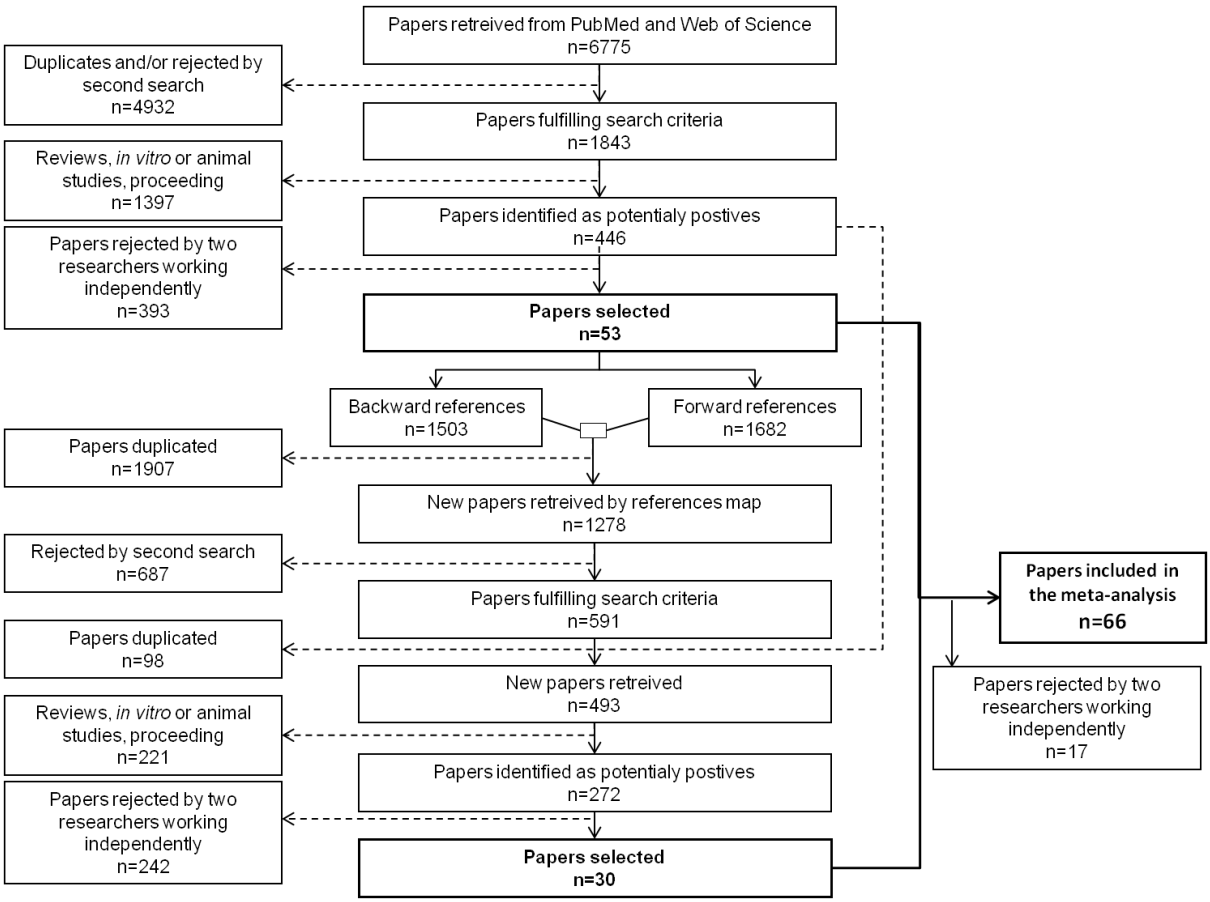

Figure. Schematic view of the literature review process. Papers were initially retrieved from Web of Science and PubMed.

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